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09/888,326	06/22/2001	George Weiner	C1039/7052 (AWS)	7237

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EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 12/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/888,326	WEINER ET AL.	
	Examiner	Art Unit	
	Jon Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 September 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,7-11,14,15,17-21,24,34,43,56 and 78-86* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,7-11,14,15,17-21,24,34,43,56 and 78-86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/01, 9/02, 1/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Action is in response to the communication filed on 09/13/04. The amendment has been entered. Claims 1, 7-11, 14, 15, 17-21, 24, 34, 43, 56 and 78-86 are currently pending in the application and are examined herein.

Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 10/1/2001, 9/30/2002 and 1/28/2004 are acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner (See attached 1449 forms).

Response to Amendment

The declaration under 37 CFR 1.132 filed 9/13/04 is acknowledged and (in view of the claim amendments) is sufficient to overcome the rejection of claims based on a non-fully enabling disclosure under 35 USC 112, first paragraph.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 7, 10, 14, 17-21 are finally rejected under 35 U.S.C. 103(a) as being unpatentable over Wooldridge et al. (Blood, 1997; 89:2994-2998; previously cited) in view of Taji et al. (Japanese Journal of Cancer Research; July 1998; Vol. 89(7), pages 748-756 for the reasons of record.

Claims 1, 7, 8, 10, 11, 14, 17-21 are finally rejected under 35 U.S.C. 103(a) as being unpatentable over Wooldridge et al. (Blood, 1997; 89:2994-2998; previously cited) in view of Winkler et al. (Blood 1999; 94(7), pages 2217-2224) for the reasons of record.

Claims 1, 7, 9, 10, 14, 17-21 are finally rejected under 35 U.S.C. 103(a) as being unpatentable over Wooldridge et al. (Blood, 1997; 89:2994-2998; previously cited) in view of Taji et al. (Japanese Journal of Cancer Research; July 1998; Vol. 89(7), pages 748-756 and further in view of Pawade et al. (Histopathology, 1995; 27(2) pages 129-137) for the reasons of record.

Claims 1, 7, 9, 10, 14, 15, 17-21 are finally rejected under 35 U.S.C. 103(a) as being unpatentable over Wooldridge et al. (Blood, 1997; 89:2994-2998; previously cited) in view of Taji et al. (Japanese Journal of Cancer Research; July 1998; Vol. 89(7), pages 748-756 and

further in view of US Patent 5,969,135 (Ramasamy et al.) for the reasons of record. It is noted that although claim 15 was not expressly indicated as rejected in the previous office action, the rejection included the Ramasamy reference, which indicates that backbone modifications can include amino acids. Furthermore, the rejection presented in the previous action stated that Wooldridge and Taji did not teach an amino acid modification of the backbone, but that Ramasamy did teach an amino acid modification of the backbone. Therefore, the rejection previously set forth did reject claim 15.

New Rejections (new claims and amended claim 56)

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 24, 34, 43, 78-81, 83, 84 and 86 are finally rejected under 35 U.S.C. 103(a) as being unpatentable over Wooldridge et al. (Blood, 1997; 89:2994-2998; previously cited) in view of US Patent 6,306,393 B1 (Goldenberg).

Wooldridge teaches a method of inhibiting the growth of a B-cell malignancy wherein an isolated synthetic immunostimulatory oligonucleotide 18 nucleotides long comprising a phosphorothioate modified backbone and an unmethylated CpG motif (see p. 2995, first column and Figure 1) was administered (300ug) to mice comprising the B-cell malignancy. Specifically, the malignant B-cells are 38C13 lymphoma cells (p. 2995, bottom of first column). The oligonucleotide treatment is followed by administration of a mouse IgG2a monoclonal antibody, specifically, MS11G6 (see p. 2994, last paragraph, the same antibody used in Example 3 of the specification p. 76-77).

Wooldridge does not specifically teach that the method can be used to treat B-cell lymphoma cells using an anti-CD19 or anti-CD22 antibody or that the B-cell malignancy is B-CLL.

Goldenberg teaches immunotherapy of B-cell malignancies using anti-CD19, anti-CD20 and anti-CD22 antibodies (e.g., see abstract, claims 1, 5, 9, 10, 22, etc.). Furthermore, the Goldenberg teaches that said antibodies can be used to treat B-cell malignancies, including B-CLL (e.g., see claims 1, 5, 14, etc.)

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to modify the methods of Wooldridge and Goldenberg in order to make a method for inhibiting the growth of B-cell lymphoma cells (including B-CLL cells and antibody resistant cells) in a subject having the B-cell lymphoma cells comprising administering to said subject the

immunostimulatory CpG nucleic acid taught by Wooldridge in combination with the CD19, CD20, or CD22 antibodies as taught by Goldenberg, with a reasonable expectation of success.

The motivation to make the indicated modification is provided by Wooldridge, who teaches that the when the oligonucleotide was used in combination with the antibody, it resulted in a synergistic effect. Specifically, Wooldridge teaches, "There was clear synergy between CpG ODN and antitumor MoAb in this model..." (See page 2997, first column) Thus indicating that the immunostimulatory CpG oligonucleotides improve the efficacy of antibody anti-tumor therapy, including tumor cells resistant to antibody therapy.

Furthermore, it would have been prima facie obvious to one of ordinary skill in the art at the time of invention to first isolate a B-cell from the patient and identify the level of the antigens CD19, CD20 or CD22 compared to normal cells before administering the therapeutic composition to the subject. As noted in *In re Aller*, 105 USPQ 233 at 235,

> "More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."

Therefore, routine optimization is not considered inventive and no evidence has been presented that the determining the level of CD19, CD20 or CD22 antigens was other than routine, that results from the optimizations have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

Claims 43 and 84-86 are finally rejected under 35 U.S.C. 103(a) as being unpatentable over Wooldridge et al. (Blood, 1997; previously cited) in view of US Patent 6,306,393 B1

(Goldenberg, previously cited) and further in view of Winkler et al. (Blood 1999, previously cited).

Wooldridge teaches a method of inhibiting the growth of a B-cell malignancy wherein an isolated synthetic immunostimulatory oligonucleotide 18 nucleotides long comprising a phosphorothioate modified backbone and an unmethylated CpG motif (see p. 2995, first column and Figure 1) was administered (300ug) to mice comprising the B-cell malignancy. Specifically, the malignant B-cells are 38C13 lymphoma cells (p. 2995, bottom of first column). The oligonucleotide treatment is followed by administration of a mouse IgG2a monoclonal antibody, specifically, MS11G6 (see p. 2994, last paragraph, the same antibody used in Example 3 of the specification p. 76-77).

Wooldridge does not specifically teach that the method can be used to treat B-cell lymphoma cells using an anti-CD19 or anti-CD22 antibody, or that the B-cell malignancy is B-CLL.

Goldenberg teaches immunotherapy of B-cell malignancies using anti-CD19, anti-CD20 and anti-CD22 antibodies (e.g., see abstract, claims 1, 5, 9, 10, 22, etc.). Furthermore, the Goldenberg teaches that said antibodies can be used to treat B-cell malignancies, including B-CLL (e.g., see claims 1, 5, 14, etc.)

Goldenberg does not teach that the anti-CD20 antibody is Rituximab.

Winkler teaches that anti-CD20 antibodies, and specifically, the anti-CD20 antibody Rituximab, can be used to inhibit the growth of B-CLL lymphoma cells which express a low

level of CD20. (e.g., see abstract, Figure 1, etc.) It is noted that Rituximab is an antibody that bind to CD20, thus Rituximab is a specific anti-CD20 antibody.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to modify the methods of Wooldridge and Goldenberg in order to make a method for inhibiting the growth of B-cell lymphoma cells (including B-CLL cells and antibody resistant cells) in a subject having the B-cell lymphoma cells comprising administering to said subject the immunostimulatory CpG nucleic acid taught by Wooldridge in combination with the CD19, CD20, or CD22 antibodies as taught by Goldenberg. Furthermore, it would have also been prima facie obvious to one of ordinary skill in the art to modify the method to use Rituximab as the anti-CD20 antibody with a reasonable expectation of success since Winkler teaches that Rituximab is an anti-CD20 antibody that can be used to treat B-cell malignancies.

The motivation to make the indicated modification is provided by Wooldridge, who teaches that the when the oligonucleotide was used in combination with the antibody, it resulted in a synergistic effect. Specifically, Wooldridge teaches, "There was clear synergy between CpG ODN and antitumor MoAb in this model..." (See page 2997, first column) Thus indicating that the immunostimulatory CpG oligonucleotides improve the efficacy of antibody anti-tumor therapy, including tumor cells resistant to antibody therapy.

Furthermore, it would have been prima facie obvious to one of ordinary skill in the art at the time of invention to first isolate a B-cell from the patient and identify the level of the antigens CD19, CD20 or CD22 compared to normal cells before administering the therapeutic composition to the subject. As noted in *In re Aller*, 105 USPQ 233 at 235,

> "More particularly, where the general conditions of a claim are disclosed in the prior art, it is

> not inventive to discover the optimum or workable ranges by routine experimentation."

Therefore, routine optimization is not considered inventive and no evidence has been presented that the determining the level of CD19, CD20 or CD22 antigens was other than routine, that results from the optimizations have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

Claims 34 and 82 are finally rejected under 35 U.S.C. 103(a) as being unpatentable over Wooldridge et al. (Blood, 1997; previously cited) in view of US Patent 6,306,393 B1 (Goldenberg, previously cited), further in view of Pawade et al. (Histopathology, 1995; previously cited).

Wooldridge teaches a method of inhibiting the growth of a B-cell malignancy wherein an isolated synthetic immunostimulatory oligonucleotide 18 nucleotides long comprising a phosphorothioate modified backbone and an unmethylated CpG motif (see p. 2995, first column and Figure 1) was administered (300ug) to mice comprising the B-cell malignancy. Specifically, the malignant B-cells are 38C13 lymphoma cells (p. 2995, bottom of first column). The oligonucleotide treatment is followed by administration of a mouse IgG2a monoclonal antibody, specifically, MS11G6 (see p. 2994, last paragraph, the same antibody used in Example 3 of the specification p. 76-77).

Wooldridge does not specifically teach that the method can be used to treat B-cell lymphoma cells using an anti-CD19 or anti-CD22 antibody, or that the B-cell malignancy is B-CLL.

Goldenberg teaches immunotherapy of B-cell malignancies using anti-CD19, anti-CD20 and anti-CD22 antibodies (e.g., see abstract, claims 1, 5, 9, 10, 22, etc.). Furthermore, the Goldenberg teaches that said antibodies can be used to treat B-cell malignancies, including B-CLL (e.g., see claims 1, 5, 14, etc.).

Neither Wooldridge nor Goldenberg teach the that B-cell malignancy is marginal zone lymphoma.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to modify the methods of Wooldridge and Goldenberg in order to make a method for inhibiting the growth of B-cell lymphoma cells (including B-CLL cells and antibody resistant cells) in a subject having the B-cell lymphoma cells comprising administering to said subject the immunostimulatory CpG nucleic acid taught by Wooldridge in combination with the CD19, CD20, or CD22 antibodies as taught by Goldenberg. Furthermore, because Pawade teaches that marginal zone lymphoma cells are CD20 positive (e.g., see abstract, etc.), it would have also been prima facie obvious to one of ordinary skill in the art that the method of using CpG oligonucleotide in combination with anti-CD20 antibody could be used to treat marginal zone lymphoma (MZL).

The motivation to make the indicated modification to treat the MZL is provided by Wooldridge, who teaches that the when the oligonucleotide was used in combination with the antibody, it resulted in a synergistic effect. Specifically, Wooldridge teaches, "There was clear synergy between CpG ODN and antitumor MoAb in this model..." (See page 2997, first column) Thus indicating that the immunostimulatory CpG oligonucleotides improve the efficacy of antibody anti-tumor therapy, including tumor cells resistant to antibody therapy.

Furthermore, it would have been prima facie obvious to one of ordinary skill in the art at the time of invention to first isolate a B-cell from the patient and identify the level of the antigens CD19, CD20 or CD22 compared to normal cells before administering the therapeutic composition to the subject. As noted in *In re Aller*, 105 USPQ 233 at 235,

> "More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."

Therefore, routine optimization is not considered inventive and no evidence has been presented that the determining the level of CD19, CD20 or CD22 antigens was other than routine, that results from the optimizations have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

Claim 56 is finally rejected under 35 U.S.C. 103(a) as being unpatentable over Wooldridge et al. (Blood, 1997; previously cited) in view of Micouin (Leukemia, 1997).

Wooldridge teaches a method of inhibiting the growth of a cancer (B-cell malignancy) wherein an isolated synthetic immunostimulatory oligonucleotide 18 nucleotides long comprising a phosphorothioate modified backbone and an unmethylated CpG motif (see p. 2995, first column and Figure 1) was administered (300ug) to mice comprising the cancer. Specifically, the malignant B-cells are 38C13 lymphoma cells (p. 2995, bottom of first column). The oligonucleotide treatment is followed by administration of a mouse IgG2a monoclonal antibody, specifically, MS11G6 (see p. 2994, last paragraph, the same antibody used in Example 3 of the specification p. 76-77).

Wooldridge does not specifically teach the method can be used to treat cancer using a human or humanized IgG1 isotype antibody.

Micouin teaches that human IgG1 antibodies can be used to treat human leukemia.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to modify the methods of Wooldridge and Micouin in order to make a method for inhibiting the growth of tumor cells in a subject having the tumor cells comprising administering to said subject the immunostimulatory CpG nucleic acid taught by Wooldridge in combination with the human IgG1 isotype antibodies taught by Micouin, with a reasonable expectation of success.

The motivation to make the indicated modification is provided by Wooldridge, who teaches that the when the oligonucleotide was used in combination with the antibody, it resulted in a synergistic effect. Specifically, Wooldridge teaches, "There was clear synergy between CpG ODN and antitumor MoAb in this model..." (See page 2997, first column) Thus indicating that the immunostimulatory CpG oligonucleotides improve the efficacy of antibody anti-tumor therapy.

Response to Arguments

Applicant's arguments filed 9/13/04 have been fully considered. Applicants arguments, in light of the amendment to the claims and the declaration under 37 CFR 1.132 (filed 9/13/04), are persuasive with respect to the rejection of claims under 35 USC 112, first paragraph. Therefore, the rejection of claims under 35 USC 112, first paragraph have been withdrawn.

However, with respect to the rejection of claims under 35 USC 103, the arguments are not persuasive.

With respect to the rejection of claims under 35 USC 103, Applicants argue:

> "Wooldridge teaches that CpG oligonucleotide plus anti-x antibody increases killing of X-expressing cells compared to either CpG oligonucleotide alone or anti-x antibody alone. The Examiner cites various references teaching that anti-Y antibody kills Y-expressing cells. The Examiner then attempts to combine these teachings with those of Wooldridge (CpG oligonucleotide plus anti-x antibody increases killing of X-expressing cells compared to either CpG oligonucleotide alone or anti-x antibody alone). An attempt to make such combinations runs directly counter to a central tenet of biology, that antigen-specific antibodies have unique specificities and are not freely interchangeable. Therefore it is plain that, without more, there is no motivation to combine the teachings of Wooldridge (CpG oligonucleotide plus anti-x antibody increases killing of X-expressing cells compared to either CpG oligonucleotide alone or anti-x antibody alone) with a teaching that anti-Y antibody kills Y-expressing cells to arrive at a result (e.g., the claimed subject matter of claim 1) that CpG oligonucleotide plus anti-Y antibody increases expression of Y and killing of Y-expressing cells. Alternatively, it is also plain that, without more, there is no motivation to combine the teachings of Wooldridge (CpG oligonucleotide plus anti-x antibody increases killing of X-expressing cells compared to either CpG oligonucleotide alone or anti-x antibody alone) with a teaching that anti-Y antibody kills Y-expressing cells to arrive at a result (e.g., the claimed subject matter of claim 1) that CpG oligonucleotide plus anti-Y antibody increases expression of X and killing of X-expressing cells." (see p. 11 of the response filed 9/13/04).

In response, it is respectfully pointed out that Wooldridge teaches "We conclude that the immunostimulatory CpG ODN can enhance antibody dependent cellular cytotoxicity [ADCC] and warrant further evaluation as potential immunotherapeutic reagents in cancer." (emphasis added; see abstract). Wooldridge also teaches, "The current studies were designed to evaluate whether CpG ODN can enhance ADCC in vitro and improve the efficacy of antitumor MoAb therapy in vivo." (see p. 2994, second column). Furthermore, Wooldridge teaches, "There was a clear synergy between CpG ODN and antitumor MoAb in this model and the most likely explanation for this finding is enhanced ADCC." (see p. 2997, first column). It is clear that

Wooldridge teaches CpG ODN can enhance antibody-dependent cellular cytotoxicity (ADCC) of antitumor monoclonal antibodies (MoAb), as such is explicitly indicated (see above).

It is particularly pointed out that although Wooldridge only exemplifies one specific antitumor antibody (IgG2a anti-idiotype MoAb) in combination with CpG ODN, Wooldridge clearly indicates that a synergistic effect can be achieved when CpG ODN is used in combination with any antitumor antibody having ADCC activity. For example, the statements, ""We conclude that the immunostimulatory CpG ODN can enhance antibody dependent cellular cytotoxicity... The current studies were designed to evaluate whether CpG ODN can enhance ADCC in vitro and improve the efficacy of antitumor MoAb therapy in vivo... There was a clear synergy between CpG ODN and antitumor MoAb in this model and the most likely explanation for this finding is enhanced ADCC" are clearly indicative that the CpG ODN in combination with any antitumor antibody having ADCC should have a synergistic effect. Furthermore, all of the references that are used in combination with Wooldridge teach antitumor antibodies that were known to have ADCC activity. Therefore, it would have been prima facie obvious to one of ordinary skill in the art that a CpG ODN could be used in combination with an antibody having ADCC activity (including the antibodies taught by the cited references) with a reasonable expectation that the combination would have a synergistic antitumor effect compared to either agent alone.

Furthermore, it is pointed out that applicants assertion "without more, there is no motivation to combine the teachings of Wooldridge... with a teaching that anti-Y antibody kills Y-expressing cells to arrive at a result (e.g., the claimed subject matter of claim 1) that CpG oligonucleotide plus anti-Y antibody increases expression of X and killing of X-expressing cells"

is not indicative of the limitations set forth in claim 1. Rather, claim 1 encompasses administration of CpG oligonucleotide plus anti-Y antibody to treat a B-cell malignancy wherein the administration increases expression of Y in the B-cell malignancy and wherein the administration increases killing of the Y-expressing cells. In view of the teachings of Wooldridge that CpG ODN used in combination with any antitumor antibody having ADCC activity will have a synergistic effect, it would have been obvious to one of ordinary skill in the art to modify Wooldridge's method by substituting any "anti-Y antibody" known to have ADCC activity (such as those claimed). Furthermore, using the concentration of CpG ODN taught by Wooldridge would necessarily result in the increased expression of "Y" in the target B-cells since the concentration of CpG used by Wooldridge is within the effective range disclosed in the specification.

Applicants also argue,

> "[P]assages contained in Wooldridge provide a teaching away from the various proposed combinations. Specifically, Wooldridge includes the following statement in the left-hand column on page 2997: 'it is unlikely that the CpG ODN has a direct effect on tumor cells, given tumor proliferation was not inhibited in vitro by CpG ODN and only minimal therapeutic benefit was seen in the group treated with CpG ODN alone.' Wooldridge goes on to say in the right hand column on page 2997, 'We detected no direct effect of the CpG ODN on 38C13 lymphoma cells...' In contrast, the instant application teaches that CpG oligonucleotides are useful in combination with particular antibodies for the very reason that the CpG oligonucleotides have an effect on the tumor cells, namely, they induce expression on the tumor cells of antigens recognized by the antibodies. Thus in view of the teaching by Wooldridge that CpG oligonucleotide has no direct effect on tumor cells, e.g., upregulation of antigen expression on tumor cells, a person of skill in the art would understand there would be no reason to combine CpG oligonucleotide with any antibody or with any cell not disclosed in Wooldridge. Wooldridge goes on to speculate, in the right-hand column of page 2997, that 'it is possible the CpG ODN induced changes in the tumor cells that rendered them more sensitive to MoAb therapy. These studies therefore need to be confirmed in another tumor model and using other CpG ODN.' Needless to say, such speculation does not provide proper foundation for making an obviousness rejection because it cannot provide a reasonable expectation of success.

In response, it is acknowledged that Wooldridge does not teach the mechanism by which the CpG/antibody treatment exerts its synergistic effect. However, Wooldridge does teach that CpG ODN enhances antibody dependent cellular cytotoxicity (ADCC) and improves therapeutic efficacy of antitumor MoAb in vivo (e.g., see abstract; p. 2994 second column; p. 2997, first column). Wooldridge also specifically teaches that the effect of using the CpG ODN in combination with antitumor MoAb is a synergistic effect (e.g., see abstract; p. 2997, first column). Based on these teachings alone, in absence of knowing the mechanism by which the synergistic effect is derived (and even considering that Wooldridge speculated that the mechanism does not involve a direct effect on the target cell) one of ordinary skill in the art would have been motivated to combine the teachings of Wooldridge with the cited references to make the claimed invention. Furthermore, the amount of CpG ODN used by Wooldridge is within the effective range disclosed in the specification. Therefore, administering the amount of CpG ODN taught by Wooldridge would necessarily result in upregulation of specifically claimed antigens. As such, it is inconsequential that Wooldridge indicates the treatment is "unlikely" to have a direct effect on the tumor cell or that more experimentation should be performed to identify the mechanism by which the treatment works. The fact that Wooldridge teaches using CpG ODN in combination with antitumor MoAb (i.e., any antitumor MoAb) results in a synergistic antitumor effect provides the required motivation for one of skill in the art and indicates a reasonable expectation of success.

Applicants also argue, "The Examiner repeatedly makes the assertion that malignant 38C13 lymphoma cells of Wooldridge are known to have a low level of CD20 expression.

However, neither Wooldridge nor any art cited by the Examiner makes any teaching whatsoever as to the level of CD20 expression by 38C13 cells."

In response, it is respectfully pointed out that the limitation that the tumor cells are "associated with a low level of CD20 expression" is only present in claim 7 and no other claim. With respect to claim 7, it is respectfully pointed out (as indicated in the previous Action) that the specification does not appear to indicate the precise definition of "associated with a low level of CD20 expression". Considering that the claim is given the broadest reasonable interpretation, the limitation is interpreted as indicating that CD20 is expressed in the cell. Given this interpretation, a cell that expresses CD20 is encompassed by the claim and a cell that does not express CD20 is not encompassed by the claim. Since the cited art teaches that the tumor cells do, in fact, express CD20 (as indicated in the previous Action), the art is considered appropriate. Furthermore, if the specification discloses a specific definition for "associated with a low level of CD20 expression", applicants are asked to identify by page and line number where the definition can be found.

With respect to the rejection of claims over Wooldridge in view of Taji, applicants argue:

"First, Applicant respectfully submits that Taji does not teach what the Examiner says it teaches. Contrary to the characterization by the Examiner, Taji teaches that anti-CD20 antibody binding sites is useful only if CD20 is expressed at a level of at least 56.5 x 10^3 per cell (Table 1), i.e., at a high level. Taji found SU-DHL-4 and SU-DHL-6 were characterized as having 123.1 x 10^3 and 86.4 x 10^3 antibody binding sites per cell (Table 1), as opposed to weakly positive cell line NALL-I (see abstract) with only 16.3 x 10^3 sites per cell (Table 1). The disclosure of Taji thus teaches that SU-DHL-4 and SU-DHL-6 cells express high levels, rather than low levels, of CD20. Significantly, Wooldridge taken alone makes no teaching whatsoever as to the level of relevant surface antigen (IgM) expressed by 38C13 cells, including no teaching that CpG oligonucleotides have any effect on the level of surface IgM expression by 38C13 cells. Similarly, Wooldridge makes no teaching whatsoever as to the level of CD20 expressed by 38C13 cells, and, as

> acknowledged by the Examiner, no teaching that CPG oligonucleotides have any effect on the level of CD20 expression by 38C13 cells. In fact, there is no teaching or suggestion provided by Wooldridge that any surface antigen expressed by B-cell malignant cells can be upregulated by contact with CpG oligonucleotide. Furthermore, with no teaching by Wooldridge that CpG oligonucleotide is effectively combined with any antibody other than the anti-idiotype antibody there disclosed, there is no suggestion or motivation either to substitute the anti-CD20 antibody of Taji for the antibody of Wooldridge, or, conversely, to add CpG oligonucleotide of Wooldridge to the anti-CD20 antibody of Taji." (see p. 13-14).

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Furthermore, with respect to the teachings of Taji, in view of the interpretation of the phrase "associated with a low level of CD20" (indicated above), the fact that Taji specifically teaches that the tumor cells express CD20 (as opposed to not expressing CD20) is sufficient to meet the limitation set forth in claim 7. It is respectfully pointed out that the limitation is not present in any claim other than claim 7.

With respect to the teachings of Wooldridge, it is respectfully pointed out that modifying the method of Wooldridge by substituting the antitumor antibody taught by Taji would result in a method of administering an CpG ODN encompassed by the claims in an amount that the specification indicates is sufficient to increase expression of the target antigen. Furthermore, contrary to applicants assertion that there is no teaching by Wooldridge that CpG oligonucleotide can be effectively combined with any antibody other than the specific anti-idiotype antibody there disclosed, Wooldridge teaches that CpG ODN can enhance antibody-dependent cellular toxicity (ADCC) (e.g., see abstract) and that there is "clear synergy between CpG ODN and

antitumor MoAb in this model and the most likely reason for this finding is enhanced ADCC." (see p. 2997). Furthermore, Wooldridge refers to ADCC and antitumor MoAb in general throughout the reference. As such, Wooldridge teaches using CpG ODN in combination with any antitumor MoAb that has an ADCC effect, not just the specific IgG2a anti-idiotype MoAb.

With respect to the rejection of claims over Wooldridge in view of Winkler, applicants argue, "Winkler discloses only the number or percentage of CD20 positive cells in the population of B-CLL patients studied, rather than the level of expression of CD20 on individual B-CLL cells... In the absence of more information than provided by Winkler, it would be incorrect to equate a low number or percentage of CD20 positive cells with low expression of CD20 because, for example, all the CD20 positive cells might express CD20 very strongly... As noted previously, Wooldridge makes no teaching whatsoever as to the level of CD20 expression by 38C13 cells, and Wooldridge does not specifically indicate or teach that oligonucleotide administration results in upregulation of CD20 expression. Without disclosure in Wooldridge or Winkler of the level of CD20 expression by 38C13 cells, or of upregulation of CD20 by CpG oligonucleotide, there is no suggestion or motivation to treat 38C13 cells with oligonucleotide and anti-CD20. Furthermore, with no teaching by Wooldridge that CpG oligonucleotide is effectively combined with any antibody other than the anti-idiotype antibody there disclosed, there is no suggestion or motivation either to substitute the anti-CD20 antibody of Winkler for the antibody of Wooldridge, or, conversely, to add CpG oligonucleotide of Wooldridge to the anti-CD20 antibody of Winkler."

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

With respect to the teachings of Winkler, in view of the interpretation of the phrase "associated with a low level of CD20" (indicated above), the fact that Winkler teaches that the tumor cells express CD20 (as opposed to not expressing CD20) is sufficient to meet the limitation set forth in claim 7. It is respectfully pointed out that the limitation is not present in any claim other than claim 7.

With respect to the Wooldridge, it is respectfully pointed out that modifying the method of Wooldridge by substituting the antitumor antibody taught by Winkler would result in a method of administering an CpG ODN encompassed by the claims in an amount that the specification indicates is sufficient to increase expression of the target antigen. Furthermore, contrary to applicants assertion that there is no teaching by Wooldridge that CpG oligonucleotide can be effectively combined with any antibody other than the specific anti-idiotype antibody there disclosed, Wooldridge teaches that CpG ODN can enhance antibody-dependent cellular toxicity (ADCC) (e.g., see abstract) and that there is "clear synergy between CpG ODN and antitumor MoAb in this model and the most likely reason for this finding is enhanced ADCC." (see p. 2997). Furthermore, Wooldridge refers to ADCC and antitumor MoAb in general throughout the reference. As such, Wooldridge teaches using CpG ODN in combination with any antitumor MoAb that has an ADCC effect, not just the specific IgG2a anti-idiotype MoAb.

With respect to the rejection of claims over Wooldridge in view of Taji and further in view of Pawade, applicants argue, "compared to the rejection on the basis of Wooldridge and Taji, the additional citation to Pawade adds only the observation that marginal zone lymphoma cells express CD20. The additional feature disclosed by Pawade does not remedy the previously noted deficiencies of the proposed combination of Wooldridge and Taji. Accordingly, there is no suggestion or motivation to make the suggested combination and therefore the Examiner has failed to make a prima facie case for rejecting the claims."

In response, it is acknowledged that Pawade only adds that marginal zone lymphoma cells express CD20. Since the applicants' arguments with respect to the rejection of claims over Wooldridge in view of Taji are not persuasive (see above), applicants' instant arguments are also not persuasive.

With respect to the rejection of claims over Wooldridge in view of Taji and further in view of Ramasamy, applicants argue, "compared to the rejection on the basis of Wooldridge and Taji, the additional citation to Ramasamy adds only the observation that the oligonucleotide can have a modified backbone. The additional feature disclosed by Ramasamy does not remedy the previously noted deficiencies of the proposed combination of Wooldridge and Taji. Accordingly, there is no suggestion or motivation to make the suggested combination and therefore the Examiner has failed to make a prima facie case for rejecting the claims."

In response, it is acknowledged that Ramasamy only adds the observation that the oligonucleotide can have a modified backbone. Since the applicants' arguments with respect to

the rejection of claims over Wooldridge in view of Taji are not persuasive (see above), applicants' instant arguments are also not persuasive.

With respect to the rejection of claims over Wooldridge in view of Goldenberg, applicants argue, "Wooldridge offers no teaching whatsoever as to expression of CD19 or C1722 by 38C13 cells. There is no basis for making the suggested combination because to do so is tantamount to equating any one antibody (e.g., the antibody of Wooldridge, directed to an irrelevant antigen) with any other antibody (e.g., the anti-CD22 antibody or the anti-CD19 antibody of Goldenberg), which is entirely contrary to the special feature of antigen-specificity that characterizes antibodies. Furthermore, with no teaching by Wooldridge that CpG oligonucleotide is effectively combined with any antibody other than the anti-idiotype antibody there disclosed, there is no motivation either to substitute the anti-CD19 or anti-CD22 antibody of Goldenberg for the antibody of Wooldridge, or, conversely, to add CpG oligonucleotide of Wooldridge to the anti-CD19 or anti-CD22 antibody of Goldenberg."

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Furthermore, contrary to applicants assertion that "there is no basis for making the suggested combination because to do so is tantamount to equating any one antibody with any other antibody, which is entirely contrary to the special feature of antigen-specificity that characterizes antibodies", Wooldridge teaches that a synergistic antitumor effect results when B-

cell malignancies are treated with CpG ODN in combination with an antitumor antibody (i.e., any antitumor antibody that has ADCC effect). Furthermore, the antibodies taught by Goldenberg were known antitumor antibodies that had an ADCC effect on tumor cells (see Goldenberg). Therefore, it would have been prima facie obvious to one of skill in the art at the time of filing to combine the references with a reasonable expectation of success.

Wit respect to the arguments against the rejection of claim 56, it is noted that the claim has been amended such that the rejection is no longer applicable. Therefore, the rejection has been withdrawn. However, the claim is rejected (necessitated by the amendment to the claim) for the reasons set forth herein.

Miscellaneous

With respect to the rejection of claims under 25 USC 103, it is noted that the rejections are based on the teaching of Wooldridge that CpG oligonucleotide used in combination with an antitumor antibody that has ADCC activity has a synergistic antitumor effect on B-cell malignancies. There is no indication that a CpG oligonucleotide used in combination with any antitumor antibody that has ADCC activity would not have a synergistic effect. A showing that the combination of CpG ODN and an antitumor antibody having ADCC activity does not result in a synergistic antitumor effect on the claimed cells would repudiate any expectation of success for modifying Wooldridge's method and would also indicate that the disclosed results are unexpected.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Mon-Fri, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon Eric Angell
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PRIMARY EXAMINER